On a nonlinear model for tumor growth: Global existence of weak solutions

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Konstantina Trivisa

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Collaborators

1. Donatella Donatelli

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A two-phase flow model

Tumor: a growing continuum $\Omega(t)$ with boundary $\partial\Omega(t)$, both of which evolve in time. The tumor region $\Omega_t := \Omega(t)$ is contained in a fixed domain B and the region $B \setminus \Omega_t$ represents the healthy tissue.

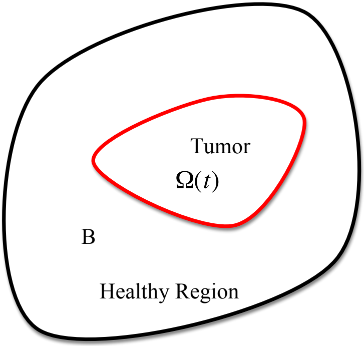

Figure: Healthy tissue - Tumor regime.

Modeling

Tumor: living cells and dead cells in the presence of a *nutrient*.

1. Living cells in *proliferating phase* or in a *quiescent phase*. Three types of cells: **proliferative cells** with density P, **quiescent cells** with density Q and **dead cells** with density D in the presence of a **nutrient** with density C.
2. Proliferating cells die as a result of *apoptosis* which is a cell-loss mechanism. Quiescent cells die in part due to *apoptosis* but mostly due to starvation.
3. Living cells undergo *mitosis*, a process that takes place in the nucleus of a dividing cell, but for proliferating cells the period of cell cycle is much shorter.

The rates of change from one phase to another are functions of the nutrient concentration C:

$$P \rightarrow Q \text{ at rate } K_Q(C),$$

$$Q \rightarrow P \text{ at rate } K_P(C),$$

$$P \rightarrow D \text{ at rate } K_A(C),$$

$$Q \rightarrow D \text{ at rate } K_D(C),$$

where K_A stands for apoptosis. Finally, dead cells are removed at rate K_R (independent of C), and the rate of cell proliferation (new births) is K_B.

There is continuous motion of cells within the tumor. This motion is characterized by the velocity field **v**, which is given by an extension of Darcy's Law known in the literature as *Brinkman's equation*

$$\nabla \sigma = -\frac{\mu}{K}\mathbf{v} + \mu \Delta \mathbf{v} \qquad (1)$$

where σ represents the pressure, μ the viscosity and K the permeability.

Governing equations of cells and nutrient

All the cells are assumed to follow the general continuity equation:

$$\frac{\partial \varrho}{\partial t} + \nabla \cdot (\varrho \mathbf{v}) = G_\varrho,$$

where ϱ may represent densities of proliferating, quiescent and dead cells. The function G includes in general proliferation, apoptosis or clearance of cells, and chemotaxis terms as appropriate.

The mass conservation laws for the densities of the proliferative cells P, quiescent cells Q and dead cells D in $\Omega(t)$ take the following form:

$$\frac{\partial P}{\partial t} + \text{div}(P\mathbf{v}) = \mathbf{G_P}, \tag{2}$$

$$\frac{\partial Q}{\partial t} + \text{div}(Q\mathbf{v}) = \mathbf{G_Q}, \tag{3}$$

$$\frac{\partial D}{\partial t} + \text{div}(D\mathbf{v}) = \mathbf{G_D}, \tag{4}$$

with

$$\begin{cases} \mathbf{G_P} = \left(K_B C - K_Q(\bar{C} - C) - K_A(\bar{C} - C)\right) P + K_P C Q \\ \mathbf{G_Q} = K_Q(\bar{C} - C)P - \left(K_P C + K_D(\bar{C} - C)\right) Q \\ \mathbf{G_D} = K_A(\bar{C} - C)P + K_D(\bar{C} - C)Q - K_R D. \end{cases} \tag{5}$$

Tumor cells consume nutrients. Nutrients diffuse into the tumor tissue from the surrounding tissue. The nutrient concentration C satisfies a linear diffusion equation of the form

$$\frac{\partial C}{\partial t} = D_1 \Delta C - \left(K_1 K_P C P + K_2 K_Q (C - \bar{C}) Q\right) C.$$

Without loss of generality, in this paper we will consider $\{\mathbf{G_P}, \mathbf{G_Q}, \mathbf{G_D}\}$ in the following simplified version:

$$\begin{cases} \mathbf{G_P} = \left(K_B C - K_Q(\bar{C} - C) - K_A(\bar{C} - C)\right) P \\ \mathbf{G_Q} = -\left(K_P C + K_D(\bar{C} - C)\right) Q \\ \mathbf{G_D} = -K_R D. \end{cases} \tag{6}$$

and for simplicity, we take (cf. Friedman 2004) ,

$$\frac{\partial C}{\partial t} = \nu \Delta C - K_C C, \tag{7}$$

where $\nu > 0$ is a diffusion coefficient and without loss of generality we consider $K_C = 1$.

The total density of the mixture is denoted by ϱ_f and is given by

$$\varrho_f = P + Q + D = Constant. \tag{8}$$

Adding (2)-(4) and taking into consideration (6)-(8) we arrive at the following relation, which represents an additional constraint

$$\begin{aligned} \rho_f \operatorname{div} \mathbf{v} =& \mathbf{G_P} + \mathbf{G_Q} + \mathbf{G_D} \\ =& (K_A + K_B + K_Q)CP - (K_A + K_Q)\bar{C}P \\ & - K_D\bar{C}Q + (K_D - K_P)C - K_R D. \end{aligned} \tag{9}$$

Boundary

The boundary of the domain Ω_t occupied by the tumor is described by means of a given velocity $\mathbf{V}(t,\mathbf{x})$, where $t \geq 0$ and $\mathbf{x} \in \mathbb{R}^3$. More precisely, assuming $\mathbf{V}$ is regular, we solve the associated system of differential equations

$$\frac{d}{dt}\mathbf{X}(t,\mathbf{x}) = \mathbf{V}(t,\mathbf{X})(t,\mathbf{x}),\ \ t > 0,\ \ \mathbf{X}(0,\mathbf{x}) = \mathbf{x},$$

and set

$$\begin{cases} \Omega_\tau = \mathbf{X}(\tau, \Omega_0),\ \text{ where } \Omega_0 \subset \mathbb{R}^3 \text{ is a given domain,} \\ \Gamma_\tau = \partial\Omega_\tau,\ \text{ and } \ Q_\tau = \{(t,x) | t \in (0,\tau), x \in \Omega_\tau\}. \end{cases}$$

We assume that the boundary Γ_τ is impermeable, meaning

$$(\mathbf{v} - \mathbf{V}) \cdot \mathbf{n}|_{\Gamma_\tau} = 0, \text{ for any } \tau \geq 0. \tag{10}$$

In addition, for *viscous* fluids, Navier proposed the boundary condition of the form

$$[\mathbb{S}\mathbf{n}]_{\text{tan}}|_{\Gamma_\tau} = 0, \tag{11}$$

with $\mathbb{S}$ denoting the viscous stress tensor which in this context is assumed to be determined through Newton's rheological law

$$\mathbb{S} = \mu\Big(\nabla \mathbf{v} + \nabla^\perp \mathbf{v} - \frac{2}{3}\,\text{div}\,\mathbf{v}\mathbb{I}\Big) + \xi\,\text{div}\,\mathbf{v}\mathbb{I},$$

where $\mu > 0$, $\xi \geq 0$ are respectively the shear and bulk viscosity coefficients.

Our aim is to show existence of global in time weak solutions to problem for any finite energy initial data.

Related works on the mathematical analysis of cancer:
Friedman *et al.* (2004), Zhao (2010) (**radially symmetric case**)
In the above articles the tumor tissue is assumed to be a porous medium and the velocity field is determined by Darcy's Law

$$\mathbf{v} = -\nabla_x \sigma \text{ in } \Omega(t).$$

Smooth solutions:

- Friedman *et al.* (2004) (small time solutions)
- Zhao (2010) (global, unique solution)

General Strategy

Penalization: of the **boundary behavior**, **diffusion** and **viscosity** in the weak formulation.

Penalization of the boundary behavior

The variational (weak) formulation of the Brinkman equation is supplemented by a singular forcing term

$$\frac{1}{\varepsilon}\int_0^T \int_{\Gamma_t} (\mathbf{v} - \mathbf{V}) \cdot \mathbf{n}\varphi \cdot \mathbf{n} dS_x dt, \quad \varepsilon > 0 \text{ small}, \tag{12}$$

penalizing the normal component of the velocity on the boundary of the tumor domain.

Penalization of the diffusion and viscosity

We introduce a **variable** shear viscosity coefficient $\mu = \mu_\omega$, as well as a **variable** diffusion $\nu = \nu_\omega$ with μ_ω, ν_ω vanishing outside the tumor domain and remaining positive within the tumor domain. In constructing the approximating problem we employ the variables ε and ω. Keeping ε and ω fixed, we solve the modified problem in a (bounded) reference domain $B \subset \mathbb{R}^3$ chosen in such way that

$$\bar{\Omega}_\tau \subset B \text{ for any } \tau \geq 0.$$

We take the initial densities (P_0, Q_0, D_0) vanishing outside Ω_0, and letting $\varepsilon \to 0$ for fixed $\omega > 0$ we obtain a "two-phase" model consisting of the *tumor region* and the *healthy tissue*.
Moreover, we prove that that the densities of cancerous cells vanish in part of the reference domain, namely $((0, T) \times B) \setminus Q_T$.
Specifically, we show that

$$(P, Q, D)(\tau, \cdot)\big|_{B \setminus \Omega_\tau} = 0 \qquad \text{for any } \tau \in [0, T].$$

Weak solutions

Definition 1. We say that $(P, Q, D, \mathbf{v}, C)$ is a weak solution of problem supplemented with boundary data satisfying (10)-(11) and initial data $(P_0, Q_0, D_0, \mathbf{v}_0, C_0)$ provided that the following hold:

- $\varrho = (P, Q, D) \geq 0$ represents a weak solution of (2)-(3)-(4) on $(0, \infty) \times \Omega$, i.e., for any test function $\varphi \in C_c^\infty(([0, T) \times \mathbb{R}^3)$, $T > 0$

$$\int_{\Omega_\tau} \varrho\varphi(\tau, \cdot)\, dx - \int_{\Omega_0} \varrho_0\varphi(0, \cdot) dx =$$

$$\int_0^\tau \int_{\Omega_t} (\varrho\partial_t\varphi + \varrho\mathbf{v} \cdot \nabla_x\varphi + \mathbf{G}_\varrho\varphi(t, \cdot))\, dxdt,$$

In particular,

$$\varrho = (P, Q, D) \in L^\infty([0, T]; L^2(\Omega)).$$

• Brinkman's equation (1) holds in the sense of distributions, i.e., for any test function $\varphi \in C_c^\infty(\mathbb{R}^3;\mathbb{R}^3)$ satisfying

$$\varphi \cdot \mathbf{n}|_{\Gamma_\tau} = 0 \text{ for any } \tau \in [0,T],$$

the following integral relation holds

$$\int_{\Omega_\tau} \sigma \,\mathrm{div}\,\varphi \,dx - \int_{\Omega_\tau} \left(\mu \nabla_x \mathbf{v} : \nabla_x \varphi + \frac{\mu}{K} \mathbf{v} \varphi \right) dx = 0. \tag{13}$$

All quantities in (13) are required to be integrable, so in particular,

$$\mathbf{v} \in W^{1,2}(\mathbb{R}^3;\mathbb{R}^3),$$

and

$$(\mathbf{v} - \mathbf{V}) \cdot \mathbf{n}(\tau,\cdot)|_{\Gamma_\tau} = 0 \text{ for a.a. } \tau \in [0,T].$$

- $C \geq 0$ is a weak solution of (7), i.e., for any test function $\varphi \in C_c^\infty(([0,T) \times \mathbb{R}^3), T > 0$ the following integral relations hold

$$\int_{\Omega_\tau} C\varphi(\tau,\cdot)\,dx - \int_{\Omega_0} C_0\varphi(0,\cdot)dx =$$

$$\int_0^\tau \int_{\Omega_\tau} C\partial_t\varphi dxdt + \int_0^\tau \int_{\Omega_t} \nu\nabla_x C\nabla_x\varphi dxdt$$

$$-\int_0^\tau \int_{\Omega_t} C\varphi(\tau,\cdot)dxdt.$$

Theorem

Let $\Omega_0 \subset \mathbb{R}^3$ be a bounded domain of class $C^{2+\nu}$ and let

$$\mathbf{V} \in C^1([0,T]; C_c^3(\mathbb{R}^3;\mathbb{R}^3))$$

be given. Let the initial data satisfy

$$P_0 \in L^2(\mathbb{R}^3),\ Q_0 \in L^2(\mathbb{R}^3),\ D_0 \in L^2(\mathbb{R}^3),\ C_0 \in L^2(\mathbb{R}^3),$$

$$(P_0, Q_0, D_0, C_0) \geq 0,\ (P_0, Q_0, D_0, C_0) \not\equiv 0$$

$$(P_0, Q_0, D_0, C_0)|_{\mathbb{R}^3 \setminus \Omega_0} = 0.$$

Then the problem (2)-(11) *with initial data as specified earlier and boundary data* (10)-(11) *admits a weak solution in the sense specified in Definition.*

Penalization scheme

We choose $R > 0$ such that

$$\mathbf{V}|_{[0,T]\times\{|\mathbf{x}|>R\}} = 0, \;\; \bar{\Omega}_0 \subset \{|\mathbf{x}| < R\}$$

and we take as the reference fixed domain

$$B = \{|\mathbf{x}| < 2R\}.$$

We introduce a variable shear viscosity coefficient $\mu = \mu_\omega(t, \mathbf{x})$ such that

$$\mu_\omega \in C_c^\infty\left([0, T] \times \mathbb{R}^3\right), \;\; 0 < \underline{\mu} \leq \mu_\omega(t, x) \leq \mu \text{ in } [0, T] \times B,$$

$$\mu_\omega = \begin{cases} \mu = const > 0 & \text{in } Q_T \\ \mu_\omega \to 0 & \text{a.e. in } ((0, T) \times B)\setminus Q_T \end{cases}$$

and a variable diffusion coefficient of the nutrient $\nu = \nu_\omega(t, \mathbf{x})$ such that

$$\nu_\omega \in C_c^\infty\left([0, T] \times \mathbb{R}^3\right), \;\; 0 < \underline{\nu} \le \nu_\omega(t, x) \le \nu \text{ in } [0, T] \times B,$$

$$\nu_\omega = \begin{cases} \nu = \mathrm{c}onst > 0 & \text{in } Q_T \\ \nu_\omega \to 0 & \text{a.e. in } ((0, T) \times B)\backslash Q_T \end{cases}$$

Finally we modify the initial data for $\varrho = (P, Q, D)$ and C in the following way

$$\varrho_0 = \varrho_{0,\omega,\varepsilon} = \varrho_{0,\omega}, \;\; \varrho_{0,\omega} \ge 0, \quad \varrho_{0,\omega} \not\equiv 0, \quad \varrho_{0,\omega}|_{\mathbb{R}^3 \backslash \Omega_0} = 0,$$

$$\int_B \varrho_{0,\omega}^2 dx \le c.$$

The weak formulation for the penalized Brinkman equation reads

$$\int_B \sigma_{\omega,\varepsilon} \operatorname{div} \varphi dx - \int_B \left(\mu_\omega \nabla_x \mathbf{v}_{\omega,\varepsilon} : \nabla_x \varphi - \mu_\omega \mathbf{v}_{\omega,\varepsilon} \varphi \right) dx + \frac{1}{\varepsilon} \int_{\Gamma_t} ((\mathbf{V} - \mathbf{v}_{\omega,\varepsilon}) \cdot \mathbf{n} \varphi \cdot \mathbf{n}) dS_x = 0 \quad (14)$$

for any test function $\varphi \in C_c^\infty(B; \mathbb{R}^3)$, where $\mathbf{v}_{\omega,\varepsilon} \in W_0^{1,2}(B; \mathbb{R}^3)$, and $\mathbf{v}_{\omega,\varepsilon}$ satisfies the no-slip boundary condition

$$\mathbf{v}_{\omega,\varepsilon}|_{\partial B} = 0 \text{ in the sense of traces.} \quad (15)$$

The weak formulation for $C_{\omega,\varepsilon}$ is as follows,

$$\int_B C_{\omega,\varepsilon}\varphi(\tau,\cdot)\,dx - \int_B C_0\varphi(0,\cdot)dx =$$

$$\int_0^\tau \int_{Bt} C_{\omega,\varepsilon}\partial_t\varphi dxdt - \int_0^\tau \int_B \nu_\omega \nabla_x C_{\omega,\varepsilon}\nabla_x\varphi dxdt$$

$$- \int_0^\tau \int_B C_{\omega,\varepsilon}\varphi(\tau,\cdot)dxdt, \tag{16}$$

for any test function $\varphi \in C_c^\infty([0,T]\times\mathbb{R}^3)$ and $C_{\omega,\varepsilon}$ satisfies the boundary conditions

$$\nabla C_{\omega,\varepsilon}\cdot\mathbf{n}|_{\partial B} = 0 \text{ in the sense of traces.} \tag{17}$$

Energy estimates

Since the vector field $\mathbf{V}$ is regular by applying the maximum principle to $C_{\omega,\varepsilon}$ and by means of Gronwall inequalities we get the following uniform bounds with respect to ε, ω.

$$\|P_{\omega,\varepsilon}\|_{L_t^\infty L_x^2 \cap L_t^2 L_x^2} + \|Q_{\omega,\varepsilon}\|_{L_t^\infty L_x^2 \cap L_t^2 L_x^2} + \|D_{\omega,\varepsilon}\|_{L_t^\infty L_x^2 \cap L_t^2 L_x^2} \leq c.$$

$$\|C_{\omega,\varepsilon}\|_{L_t^2 L_x^2} + \nu_\omega \|\nabla C_{\omega,\varepsilon}\|_{L_t^2 L_x^2} \leq c,$$

where c is depends only on the initial data and $L_t^q L_x^p$ stands for $L^q(0, T; L^p(B))$.

The earlier analysis yields

$$\operatorname{div} \mathbf{v}_{\omega,\varepsilon} = \mathbf{G}, \qquad \text{with } \mathbf{G} \in L^2(0, T; L^2(B)). \tag{18}$$

$$\Downarrow$$

$$\|\nabla \mathbf{v}_{\omega,\varepsilon}\|_{L^2_x} \leq c \|\mathbf{G}\|_{L^2_x}. \tag{19}$$

By a standard application of elliptic regularity theory (c.f. Lions (1998)) we get

$$\|\sigma_{\omega,\varepsilon}\|_{L^2_x} \leq c, \tag{20}$$

uniformly with respect to ε, ω.

Since the vector field $\mathbf{V}$ vanishes on the boundary of the reference domain B it may be used as a test function in the weak formulation of Brinkman's equation for the penalized problem (14), namely

$$\int_B \sigma_{\omega,\varepsilon} \operatorname{div} \mathbf{V} dx - \int_B \big(\mu_\omega \nabla_x \mathbf{v}_{\omega,\varepsilon} : \nabla_x \mathbf{V} - \mu_\omega \mathbf{v}_{\omega,\varepsilon} \mathbf{V}\big) dx + \frac{1}{\varepsilon} \int_{\Gamma_t} ((\mathbf{V} - \mathbf{v}_{\omega,\varepsilon}) \cdot \mathbf{n} \mathbf{V} \cdot \mathbf{n}) dS_x = 0. \tag{21}$$

$$\Downarrow$$

$$\mu_\omega \int_B (|\nabla_x \mathbf{v}_{\omega,\varepsilon}|^2 + \mathbf{v}_{\omega,\varepsilon}^2) dx + \frac{1}{\varepsilon} \int_{\Gamma_t} |(\mathbf{v}_{\omega,\varepsilon} - \mathbf{V}) \cdot \mathbf{n}|^2 dS \leq$$

$$\int_B \left(\mu_\omega \nabla_x \mathbf{v}_{\omega,\varepsilon} : \nabla_x \mathbf{V} + \mu_\omega \mathbf{v}_{\omega,\varepsilon} \mathbf{V}\right) dx + \int_B \sigma_{\omega,\varepsilon} \left(\operatorname{div} \mathbf{v}_{\omega,\varepsilon} - \operatorname{div}_x \mathbf{V}\right) dx. \tag{22}$$

Since the vector field $\mathbf{V}$ is smooth by means (18), (20), we get the following uniform bounds with respect to ε, ω.

$$\mu_\omega \|\mathbf{v}_{\omega,\varepsilon}\|_{L^2_x} + \mu_\omega \|\nabla \mathbf{v}_{\omega,\varepsilon}\|_{L^2_x} \leq c, \tag{23}$$

$$\int_{\Gamma_t} |(\mathbf{v}_{\omega,\varepsilon} - \mathbf{V}) \cdot \mathbf{n}|^2 dS \leq c\varepsilon. \tag{24}$$

Singular limits

Main Goal: Get rid of the quantities that are supported by the healthy tissue $B \setminus \Omega_t$

1. (a) Vanishing penalization $\varepsilon \to 0$
2. (b) Vanishing density terms on the healthy tissue
3. (c) Vanishing viscosity limit $\omega \to 0$.

Vanishing Penalization

$$\varrho_{\omega,\varepsilon} \to \varrho_\omega \quad \text{in} \quad C_{\text{weak}}(0,T;L^2(B)) \tag{25}$$

From the energy estimates presented above we get

$$\begin{aligned} \mathbf{v}_{\omega,\varepsilon} \to \mathbf{v}_\omega \quad \text{weakly in } L^2(0,T;W_0^{1,2}(B)) \\ C_{\omega,\varepsilon} \to C_\omega \quad \text{weakly in } L^2(0,T;W_0^{1,2}(B)) \end{aligned} \tag{26}$$

while

$$(\mathbf{v}_{\omega,\varepsilon} - \mathbf{V}) \cdot \mathbf{n}(\tau,\cdot)\big|_{\Gamma_\tau} = 0 \quad \text{for a.a } \tau \in [0,T].$$

Taking into consideration the earlier analysis and the compact embedding of $L^2(B)$ in $W^{-1,2}(B)$ we get

$$\varrho_{\omega,\varepsilon} \to \varrho_\omega \quad \text{in} \quad C_{\text{weak}}(0,T;L^2(B))$$

$$\mathbf{v}_{\omega,\varepsilon} \to \mathbf{v}_\omega \quad \text{weakly in } W_0^{1,2}(B)$$

$$C_{\omega,\varepsilon} \to C_\omega \quad \text{weakly in } L^2(0,T;W_0^{1,2}(B))$$

$$(\mathbf{v}_{\omega,\varepsilon} - \mathbf{V}) \cdot \mathbf{n}(\tau,\cdot)\big|_{\Gamma_\tau} = 0 \quad \text{for a.a } \tau \in [0,T].$$

$$\varrho_{\omega,\varepsilon}\mathbf{v}_{\omega,\varepsilon} \to \varrho_{\omega}\mathbf{v}_{\omega} \quad \text{in} \quad C_{\text{weak}}([T_1, T_2]; L^{2q/q+2}(B)).$$

$$\mathbf{v}_{\omega,\varepsilon} \otimes \mathbf{v}_{\omega,\varepsilon} \to \mathbf{v}_{\omega} \otimes \mathbf{v}_{\omega} \quad \text{weakly in } L^{6q/6+q}(B)$$

$$\varrho_{\omega,\varepsilon} C_{\omega,\varepsilon} \to \varrho_{\omega} C_{\omega} \quad \text{weakly} - (*) \text{ in} \quad L^{\infty}(0, T; L^{2q/q+2}(B)).$$

$$2 < q \leq 6.$$

Passing into the limit in the weak formulation (14) of the Brinkman's equation we get

$$\int_B \sigma_\omega \operatorname{div} \varphi dx - \int_B \left(\mu_\omega \nabla_x \mathbf{v}_\omega : \nabla_x \varphi - \mu_\omega \mathbf{v}_\omega \varphi\right) dx = 0, \qquad (27)$$

for any test function $\varphi \in C_c^\infty(B; \mathbb{R}^3)$, $\varphi \cdot \mathbf{n}|_B = 0$.
Next, for $\varrho_\omega \equiv (P, Q, D)$,

$$\int_B \varrho_\omega \varphi(\tau, \cdot) dx - \int_B \varrho_0 \varphi(0, \cdot) dx = \int_0^\tau \int_B \left(\varrho_\omega \partial_t \varphi + \varrho_\omega \mathbf{v} \cdot \nabla_x \varphi + \mathbf{G}_{\varrho_\omega} \varphi(t, \cdot)\right) dxdt$$

The evolution of the interface Γ_t

The interface Γ_t can be identified with a component of the

$$\textbf{level set} \quad \{\Phi(\tau, \cdot) = 0\}$$

The sets $B \setminus \Omega_\tau$ correspond to the set $\{\Phi(\tau, \cdot) > 0\}$.
$\Phi = \Phi(t, x)$: the unique solution of the transport equation

$$\boxed{\partial_t \Phi + \nabla_x \Phi(t, x) \cdot \mathbf{V} = 0}$$

$$\Phi_0(x) = \begin{cases} > 0 & \text{for } x \in B \backslash \Omega_0, \\ < 0 & \text{for } x \in \Omega_0 \cup (\mathbb{R}^3 \backslash \overline{B}), \end{cases} \qquad \nabla_x \Phi_0 \neq 0 \text{ on } \Gamma_0.$$

Finally,

$$\nabla_x \Phi(\tau, x) = \lambda(\tau, x) \mathbf{n}(x) \qquad \text{for any } x \in \Gamma_\tau$$

$$\lambda(\tau, x) \geq 0 \qquad \text{for } \tau \in [0, T].$$

Lemma. Let $\varrho \in L^\infty(0,T; L^2(B))$, $\varrho \geq 0$, $\mathbf{v} \in L^2(0,T; W_0^{1,2}(B))$ satisfying the following equation

$$\int_B \big(\varrho\varphi(\tau,\cdot) - \varrho_0\varphi(0,\cdot)\big)\,dx = \int_0^\tau \int_B \big(\varrho\partial_t\varphi + \varrho\mathbf{v}\cdot\nabla_x\varphi + \mathbf{G}_\varrho\varphi(t,\cdot)\big)\,dxdt, \tag{28}$$

for any $\tau \in [0,T]$ and any test function $\varphi \in C_c^1([0,T]\times\mathbb{R}^3)$ and $\mathbf{G}_\varrho \in L^\infty(0,T; L^2(B))$.

Moreover assume that

$$(\mathbf{v} - \mathbf{V})(\tau, \cdot) \cdot \mathbf{n}\Big|_{\Gamma_\tau} = 0 \qquad \text{a.e. } \tau \in (0, T) \tag{29}$$

and that

$$\varrho_0 \in L^2(\mathbb{R}^3), \qquad \varrho_0 \geq 0 \qquad \varrho_0\Big|_{B \setminus \Omega_0} = 0.$$

Then

$$\varrho(\tau, \cdot)\Big|_{B \setminus \Omega_\tau} = 0 \qquad \text{for any } \tau \in [0, T].$$

Proof:

For given $\eta > 0$ we use

$$\varphi = \left[\min\left\{\frac{1}{\eta}\Phi; 1\right\}\right]^{+}$$

as a test function in the weak formulation (28) and we obtain

$$\int_{B\setminus\Omega_\tau} \varrho\varphi \, dx = \frac{1}{\eta}\int_0^\tau \int_{\{0\le\Phi(t,x)\le\eta\}} (\varrho\partial_t\Phi + \varrho\mathbf{v}\cdot\nabla_x\Phi + \mathbf{G}_\varrho\Phi)\, dxdt. \tag{30}$$
$$+ \int_0^\tau \int_{\{\Phi(t,x)>\eta\}} \mathbf{G}_\varrho dxdt$$

We have that

$$\varrho\partial_t\Phi + \varrho\mathbf{v}\cdot\nabla_x\Phi = \varrho(\partial_t\Phi + \mathbf{v}\cdot\nabla_x\Phi) = \varrho(\mathbf{v}-\mathbf{V})\cdot\nabla_x\Phi.$$

$$(\mathbf{v}-\mathbf{V})\cdot\nabla_x\Phi \in W_0^{1,2}(B\setminus\Omega_\tau) \quad \text{for a.e. } t\in(0,\tau). \tag{31}$$

$$\delta(t,x) = dist_{\mathbb{R}^3}[x, \partial(B \backslash \Omega_\tau)] \qquad \text{for } t \in [0,\tau],\ x \in B \backslash \Omega_\tau, \qquad (32)$$

$$\Downarrow$$

$$\frac{1}{\delta}(\mathbf{V} - \mathbf{v}) \cdot \nabla_x \Phi \in L^2([0,\tau] \times B \backslash \Omega_\tau).$$

Since **V** is regular we have that

$$\frac{\delta(t,x)}{\eta} \leq c, \qquad \frac{\sqrt{\delta(t,x)}}{\eta} \leq c \qquad \text{when } 0 \leq \Phi(t,x) \leq \eta. \qquad (33)$$

$$\int_{B\setminus\Omega_\tau} \varrho\varphi dx \le \frac{1}{\eta}\int_0^\tau \int_{\{0\le\Phi(t,x)\le\eta\}} \delta \frac{\varrho(\mathbf{V}-\mathbf{u})\cdot\nabla_x\Phi}{\delta} dxdt$$
$$+\frac{1}{\eta}\int_0^\tau \int_{\{0\le\Phi(t,x)\le\eta\}} \sqrt{\delta}\frac{\mathbf{G}_\varrho}{\sqrt{\delta}}\Phi dxdt$$
$$+\int_0^\tau \int_{B\setminus\Omega_t} \mathbf{G}_\varrho\, dxdt$$

Letting $\eta \to 0$ and using $\varrho, \mathbf{G}_\varrho \in L^\infty(0,T;L^2(B))$

$$\Downarrow$$

$$\int_{B\setminus\Omega_\tau} \varrho\; dx = 0.$$

Next, we let $\omega \to 0$ and we obtain the result. In particular,

$$\int_{B \setminus \Omega_t} \sigma_\omega \mathrm{div}\phi \, dxdt = 0.$$

Current and future directions

- On a nonlinear model for the evolution of tumor growth with a variable total density of cancerous cells.

$$\varrho_f = \varrho_f(x,t) = [P+Q+D](x,t)$$

$$\partial_t(\varrho_f \mathbf{v}) + \mathrm{div}(\varrho_f \mathbf{v} \otimes \mathbf{v}) = -\nabla\sigma + \mu\Delta\mathbf{v} - \frac{\mu}{K}\mathbf{v}$$

- On a nonlinear mixed-type model for the evolution of tumor growth in the presence of drug resistance.
  - Long time dynamics, singular limits: comparison with experimental evidence
- Can we view the model presented in this talk as a Gradient Flow Model?

- Construct a **three** level approximating scheme based on **penalization** of the boundary behavior ε , **penalization** of diffusion and viscosity ω, and the addition of the **artificial pressure** δ.
- Establish the strong convergence of the density.
- Establish higher integrality of pressure. We show that

$$\int \int_K (\sigma(\varrho_f)\varrho_f^{\nu} + \delta \varrho_f^{\beta+\nu})\, dxdt \leq c(K) \text{ for a certain } \nu.$$

- Extend the class of test functions.

$$\partial_t(\varrho_f \mathbf{v}) + \operatorname{div}(\varrho_f \mathbf{v} \otimes \mathbf{v}) = -\nabla\sigma + \mu \operatorname{div} \mathbb{S} - \frac{\mu}{K}\mathbf{v}$$

The weak formulation for the momentum equation of the penalized problem reads:

$$\int_B \varrho_f \mathbf{v} \cdot \varphi(\tau, \cdot)\, dx - \int_B (\varrho_f \mathbf{v})_0 \cdot \varphi(0, \cdot)\, dx$$

$$= \int_0^\tau \int_B \Big(\varrho_f \mathbf{v} \cdot \partial_t \varphi + \varrho_f [\mathbf{v} \otimes \mathbf{u}] : \nabla_x \varphi + \sigma(\varrho_f) \operatorname{div}_x \varphi + \delta \varrho_f^\beta \operatorname{div}_x \varphi$$

$$-\mu_\omega \left(\nabla_x \mathbf{v} + \nabla_x \mathbf{v} - \frac{2}{3} \operatorname{div}_x \mathbf{v} \mathbb{I} \right) : \nabla_x \varphi \Big)\; dxdt$$

$$+\frac{1}{\varepsilon} \int_0^\tau \int_{\Gamma_t} ((\mathbf{V} - \mathbf{v}) \cdot \mathbf{n} \varphi \cdot \mathbf{n}) dS_x dt$$

Effective viscous pressure

Basic idea: “Compute” the pressure in the momentum equation. Formally,

$$\sigma - \nabla_x \Delta^{-1} \nabla_x : \mathbb{S} = -\nabla_x \Delta^{-1} \nabla_x : (\varrho_f \mathbf{v} \otimes \mathbf{v}) - \Delta^{-1} \mathrm{div}_x (\partial_t (\varrho_f \mathbf{v})).$$

Newton's law implies

$$\nabla_x \Delta^{-1} \nabla_x : \mathbb{S} = \left(\frac{4\mu}{3} + \xi \right) \mathrm{div}_x \mathbf{v}$$

The quantity

$$\sigma - \nabla_x \Delta^{-1} \nabla_x : \mathbb{S} = \sigma - \left(\frac{4}{3} + \eta \right) \mathrm{div}_x \mathbf{v}$$

effective viscous pressure.

Strong convergence of the density

The crucial observation is the effective viscous pressure identity:

$$\overline{\sigma_\delta(\varrho_f) T_k(\varrho_f)} - \overline{\sigma_\delta(\varrho_f)}\, \overline{T_k(\varrho_f)} = \frac{4}{3}\mu_\omega \left(\overline{T_k(\varrho_f) \operatorname{div} \mathbf{v}} - \overline{T_k(\varrho_f)} \operatorname{div}_x \mathbf{v} \right).$$

$$\sigma_\delta(\varrho_f) = \sigma(\varrho_f) + \delta \varrho_f^\beta, \;\; T_k(\varrho_f) = ?.$$

Higher integrability of the pressure. Concentration phenomena

Energy inequality $\quad \rightarrow \quad \sigma \in L^1((0,T)\times\Omega)$

One can obtain better estimates via the

- multipliers technique (Feireisl, Lions)
- use $\quad \varphi(t,x) = \psi(t) B[\varrho_f^\nu] \; \psi \in \mathcal{D}(0,T)$

as test functions in the weak formulation of the momentum eq.

B[v] $\quad$ solns to

$$\begin{cases} div(B[v]) = v - \frac{1}{|\Omega|}\int_\Omega v dx \\ B[v]|_{\partial\Omega} = 0 \end{cases}$$

$$\Downarrow$$

$$\int_0^T \int_\Omega \sigma \varrho_f^\nu \, dxdt < C.$$

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